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**Toxicology and Carcinogenesis Studies of  
Bis(2-chloroethoxy)methane (CEM)  
in F344/N Rats and B6C3F1 Mice  
(Dermal studies)**

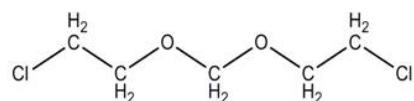
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NTP Board of Scientific Counselors  
Technical Reports Subcommittee  
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## Bis(2-chloroethoxy)methane

- Nominated by NIEHS because high production chemical with no chronic toxicity/carcinogenesis data
  - Production volume 25-46 million pounds per year
  - Starting material to produce polysulfide elastomers
  - Used in sealant applications because of resistance to degradation



**CAS No. 111-911**

**C<sub>5</sub>H<sub>10</sub>Cl<sub>2</sub>O<sub>2</sub>**

**MW: 173.04**



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## Genotoxicity Test Results

- Weak mutagenicity with S9 activation in multiple bacterial stains
- Micronucleus test, male and female mice – negative (3-month study)
- Micronucleus test, male rats – negative (3-day study)



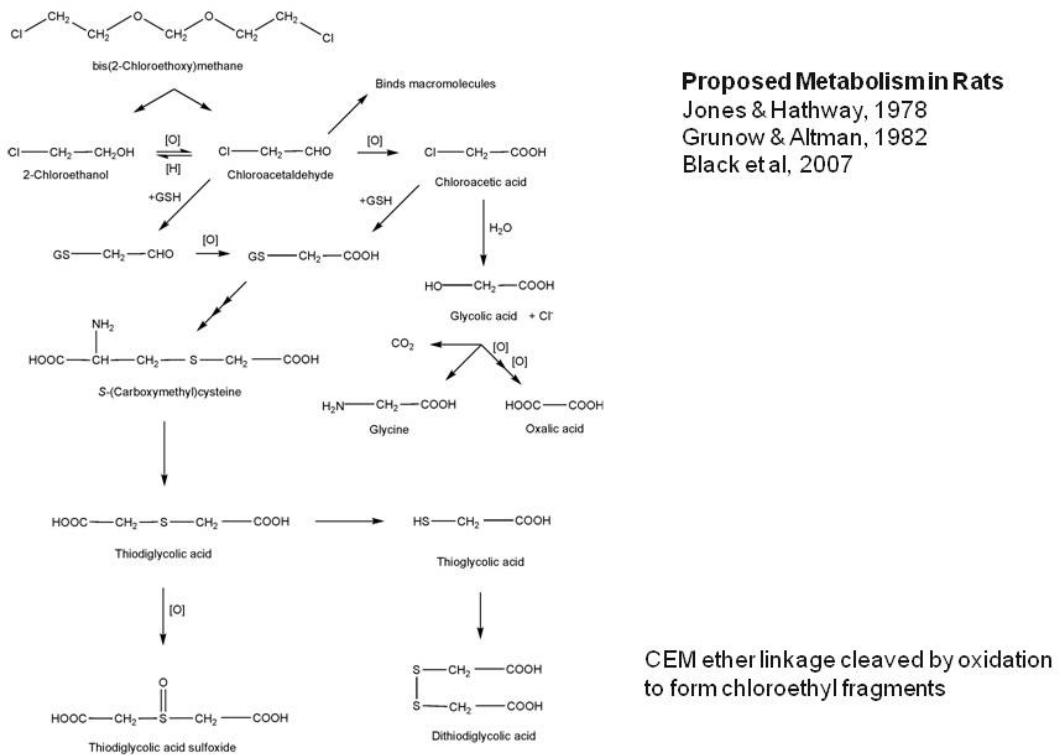
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## Absorption of CEM

(0.1 - 10 mg/kg)

- Rats (10 wk old rats)
  - 15% of a 10 mg/kg dose absorbed dermally (when skin is protected)
  - 40 - 44% of dose absorbed when skin is not protected (oral administration possible)
  - Thioglycolic acid (TDGA) was the major metabolite (40% of dose) in urine
- Mice (10 wk old mice)
  - 18% of a 10 mg/kg dose absorbed dermally (when skin is protected)
  - 21% of a 10 mg/kg dose absorbed when skin is not protected (oral administration possible)
  - TDGA was not detected in urine (TDGA was detected in plasma in Toxicokinetic Study)
  - Mice metabolize CEM more rapidly than rats





## Bis(2-chloroethoxy)methane Experimental Design

<b>Study Animals:</b>	Male & Female F344/N Rats & B6C3F <sub>1</sub> Mice
<b>Route:</b>	Dermal (ethanol)
<b>14-day studies:</b>	0, 12.5, 25, 50, 100, or 200 mg/kg 5 animals/species/sex/dose
<b>13-week studies:</b>	0, 50, 100, 200, 400, 600 mg/kg 10 animals/species/sex/dose
<b>2-Year studies:</b>	Male & Female Rats: 0, 75, 100, 300 mg/kg Male Mice: 0, 150, 300, 600 mg/kg Female Mice: 0, 100, 200, 400 mg/kg 50 animals/species/sex/dose



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### 13-week CEM Study - Survival - Rats

mg/kg	0	50	100	200	400	600
<b>Male Rat</b>	10	10	10	10	10	0
Week of Death						1, 1, 1, 1, 6, 7, 7, 8, 8, 10
<b>Female Rat</b>	10	10	10	10	8	0
Week of Death					11, 11	4, 4, 5, 5, 5, 5, 6, 6, 6

N = 10 per group



### 13-week CEM Study - Male Rats - Heart lesions

mg/kg	0	50	100	200	400	600
Myocardium Cytoplasmic vacuolization	0	0	0	0	6** (1.3) <sup>a</sup>	10** (1.5)
Myocardium Mononuclear cell infiltration	0	0	0	0	7** (1.0)	10** (1.4)
Myocardium Necrosis	0	0	0	0	0	7** (1.7)
Atrial thrombosis	0	0	0	0	0	3 (3.7)

\*\* p<0.01

<sup>a</sup>severity of lesion

N = 10 per group



### 13-week CEM Study - Female Rats – Heart lesions

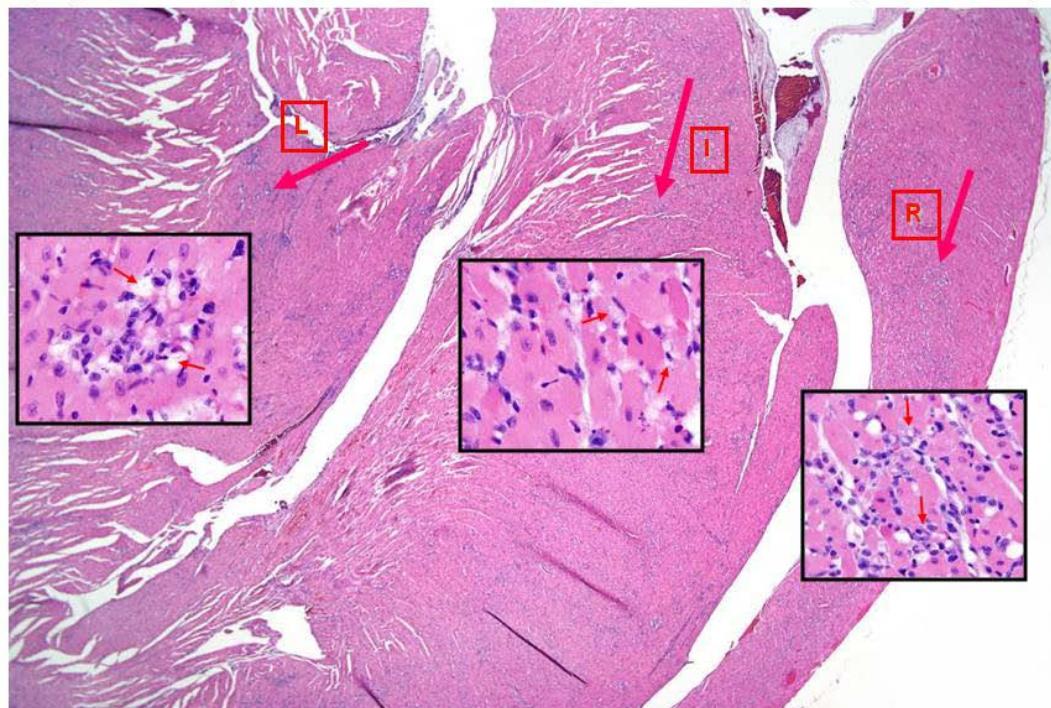
mg/kg	0	50	100	200	400	600
Myocardium Cytoplasmic vacuolization	0	0	0	2 (1.0) <sup>a</sup>	5* (1.4)	9** (1.8)
Myocardium Mononuclear cell Infiltration	0	0	0	7** (1.0)	6** (1.2)	10** (1.9)
Myocardium Necrosis	0	0	0	1 (1.0)	1 (1.0)	5* (1.4)

\*p<0.05; \*\* p<0.01

<sup>a</sup>severity of lesion

N = 10 per group

**CEM heart damage seen throughout heart:  
Vacuolization, and Mononuclear Cell Infiltration  
600 mg/kg F344 rat: (L-left ventricle; I-interventricular septa; R-right ventricle)**





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### 13-week CEM Study - Survival - Mice

mg/kg	0	50	100	200	400	600
<b>Male Mouse</b>	10	10	10	10	10	10
<b>Female Mouse</b>	10	10	10	10	10	7
Week of Death						6,7,11

N = 10 per group



### 13-week CEM study- Female Mice - Heart lesions

mg/kg	0	50	100	200	400	600
Myocardium Cytoplasmic vacuolization	0	0	0	0	4* (1.0) <sup>a</sup>	5* (1.6)

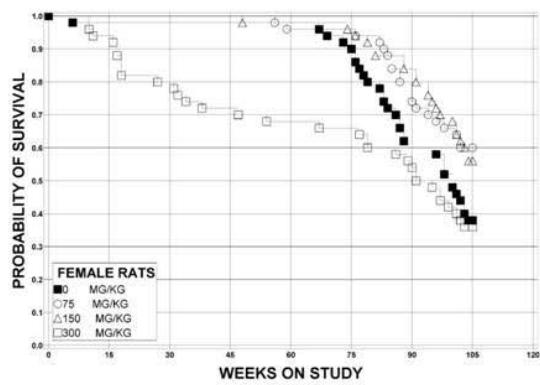
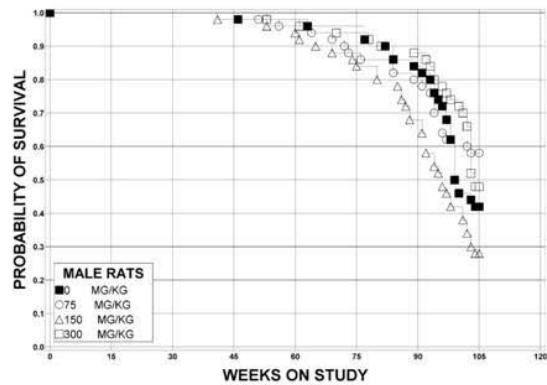
\*p<0.05

<sup>a</sup>severity of lesion

N = 10 per group

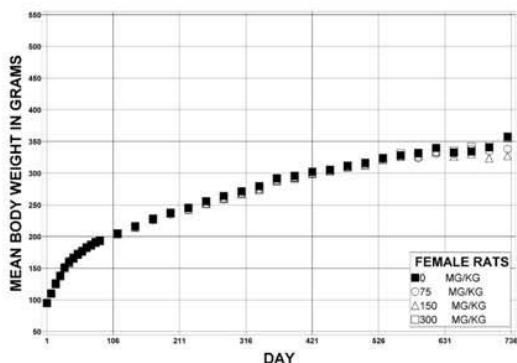
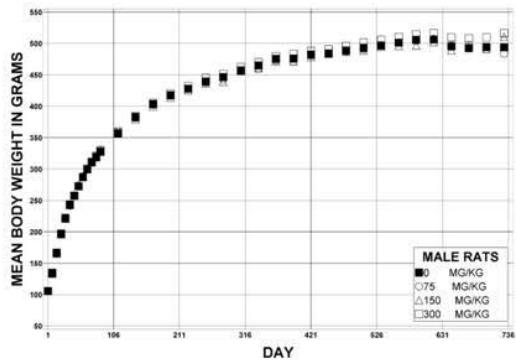


## Survival - 2-year Rat Study





## Body Weights - 2-year Rat Study





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## 2-year Study - Male Rat - Nose and Forestomach lesions

mg/kg	0	75	100	300
Nose: Olfactory epithelium degeneration	5 (1.2) <sup>a</sup>	17** (1.3)	30** (1.3)	48** (1.9)
Forestomach: Inflammation	0	2 (3.5)	6* (3.3)	10** (2.6)
Ulcer	0	2 (3.5)	2 (4.0)	7** (3.0)

\*p<0.05; \*\* p<0.01

<sup>a</sup>severity of lesion

N = 49-50 per group



## 2-year Study - Female Rat - Adrenal and Nose lesions

mg/kg	0	75	100	300
Adrenal cortex necrosis	0	0	0	7** (2.6) <sup>a</sup>
Nose: olfactory epithelium degeneration	5 (1.0)	4 (1.3)	18** (1.1)	49** (2.3)

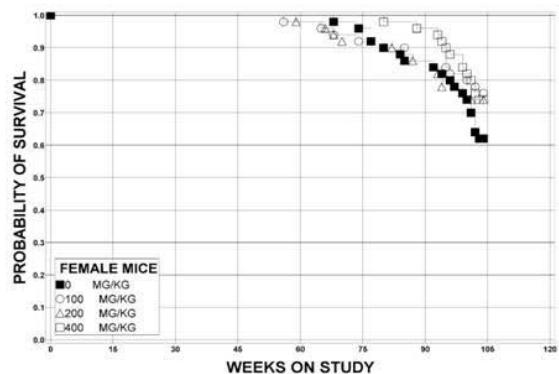
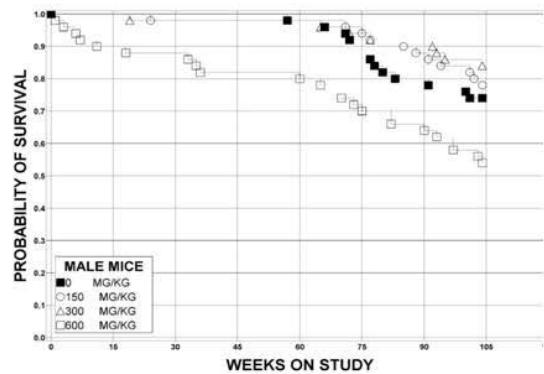
\*\* p<0.01

<sup>a</sup>severity of lesion

N=49-50 per group

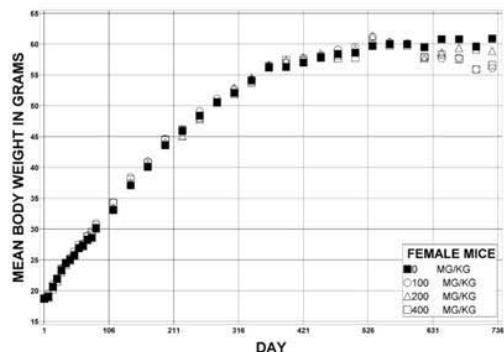
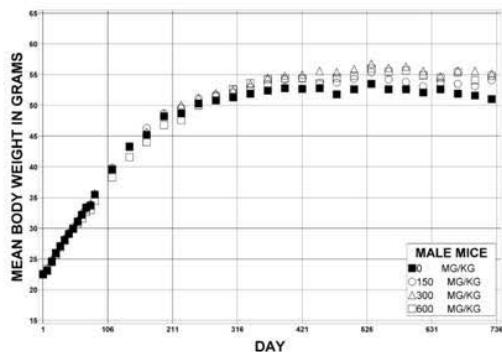


## Survival - 2-year Mouse Study





## Body Weights - 2-year Mouse Study





## 2-year Study - Male Mouse - Heart lesions

mg/kg	0	150	300	600
Cardiomyopathy	10 (1.0) <sup>a</sup>	12 (1.1)	7 (1.0)	28** (1.4)
Myocardium fibrosis	0	3 (1.0)	3 (1.0)	13** (1.1)
Myocardium Mononuclear cell infiltration	11 (1.0)	12 (1.1)	8 (1.0)	28** (1.4)
Myocardium cytoplasmic vacuolization	10 (1.0)	15 (1.1)	11 (1.0)	29** (1.3)

\*\* p<0.01

<sup>a</sup>severity of lesion

N = 50 per group



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## 2-year Study - Female Mouse - Heart lesions

mg/kg	0	100	200	400
Cardiomyopathy	10 (1.2) <sup>a</sup>	7 (1.0)	10 (1.0)	17 (1.1)
Myocardium Mononuclear cell infiltration	9 (1.2)	7 (1.0)	10 (1.0)	17 (1.1)
Myocardium Cytoplasmic vacuolization	14 (1.1)	4** (1.0)	6* (1.0)	13 (1.1)

\*p<0.05; \*\* p<0.01

<sup>a</sup>severity of lesion

N = 50 per group



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## 2-year Study - Male Mouse - Skin, Forestomach and Stomach lesions

mg/kg	0	150	300	600
Skin: site of application - dermis fibrosis	6 (1.7) <sup>a</sup>	1* (3.0)	2 (3.0)	25** (1.3)
Skin: site of application - dermis inflammation	3 (2.3)	1 (3.0)	3 (2.0)	13** (1.4)
Skin: site of application - epidermis hyperplasia	8 (1.8)	1* (2.0)	4 (1.8)	28** (1.2)
Forestomach ulcer	1	1	1	7*

\*p<0.05; \*\* p<0.01

<sup>a</sup>severity of lesion

N = 50 per group



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## Conclusions

- Male Rats: **No** evidence of carcinogenic activity
- Female Rats: **No** evidence of carcinogenic activity
- Male Mice: **No** evidence of carcinogenic activity
- Female Mice: **No** evidence of carcinogenic activity
- Administration of CEM for 2-years resulted in increased incidences of nonneoplastic lesions of the:
  - Nose, in Male and Female Rats
  - Forestomach, in Male Rats
  - Heart, in Male and Female Mice
  - Forestomach and Skin, in Male Mice